

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

Applicants	: Molino et al.	)	Examiner:
		)	Marcela M. Cordero
Serial No.	: 10/802,013	)	Garcia
		)	
Cnfrm. No.	: 4932	)	Art Unit:
		)	1654
Filed	: March 16, 2004	)	
		)	
For	: NOVEL CYCLOSPORINS	)	
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SUPPLEMENTAL DECLARATION OF BRUCE F. MOLINO, PH.D.  
UNDER 37 CFR § 1.132

**Mail Stop:**

Commissioner for Patents

P.O. Box 1450

Alexandria, Virginia 22313-1450

Dear Sir:

I, Bruce F. Molino, Ph.D., pursuant to 37 CFR § 1.132, declare:

1. I received a B.S. degree in Chemistry from Rutgers University in 1977 and a Ph.D. degree in Organic Chemistry from the University of Maryland in 1984.

2. I am the Senior Director of the Medicinal Chemistry Department at AMRI.

3. It is my understanding that the above application is assigned to AMR Technology, Inc. which is a subsidiary of AMRI.

4. I am a co-inventor of the above application.

5. I am submitting this declaration to show immunosuppressivity data for compounds of the present application.

6. Example 116 of the above application describes several biological test methods that were used to determine immunosuppressive activity for compounds of that application. The immunosuppressive activity data for these compounds is set forth below in Table 1. Compounds are identified by the Example number of my above application. The extent of inhibition of murine splenocyte proliferation is obtained by measuring the inhibition of [<sup>3</sup>H]-thymidine uptake that occurs upon splenocyte stimulation in the one-way mixed

lymphocyte reaction (MLR) or splenocyte stimulation with the plant-derived mutagen Concanavilin (ConA).

<b>Table I. Immunosuppressive Activity</b>					
<i>Patent Compound Example#</i>	<i>Assay Mode of Splenocyte Stimulation</i>	<i>% Inhibition [<sup>3</sup>H]-thymidine uptake @ 0.10 µg/mL</i>	<i>% Inhibition [<sup>3</sup>H]-thymidine uptake @ 1.0 µg/mL</i>	<i>IC<sub>50</sub> µg/mL</i>	<i>Inhibition by positive control (CsA) IC<sub>50</sub> µg/mL</i>
20	MLR		67%	< 1.0	0.011
21	MLR	13%		> 0.10	0.008
27	MLR		88%	< 1.0	0.015
33	MLR			0.10	0.020
37	ConA	35%		> 0.10	0.007
50	ConA	50%		~ 0.10	0.007
51	MLR	27%	91%	< 1.0	0.016
53	MLR	31%		> 0.10	0.023
55	MLR	25%	52%	~ 1.0	0.030
57	MLR	20%		> 0.10	0.020
59	MLR	35%		> 0.10	0.023
63	MLR		95%	< 1.0	0.016
65	MLR	33%		> 0.10	0.016
84	MLR	29%		> 0.10	0.016
100	MLR	27%		> 0.10	0.016
104	MLR	32%		> 0.10	0.011

7. The IC<sub>50</sub> values for the positive control are the concentration of the positive control (cyclosporin A) that inhibit [<sup>3</sup>H]-thymidine uptake by 50%, which may be compared with the percent inhibition for test compounds at 0.1 µg/mL and 1.0 µg/mL test concentrations.

8. I hereby declare that all statements made herein of my own knowledge are true and that all statements made on information and belief are believed to be true; and further that these statements were made with the knowledge that willful false statements and the like so

made are punishable by fine or imprisonment, or both, under section 1001 of Title 18 of the United States Code, and that such willful false statements may jeopardize the validity of the application or any patent issuing thereon.

Date: April 16, 2008

Bruce F. Molino  
Bruce F. Molino, Ph.D.